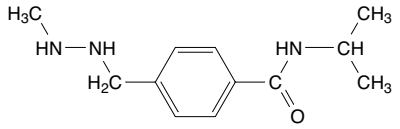
Procarbazine and Its Hydrochloride

CAS Nos. 671-16-9 and 366-70-1

Reasonably anticipated to be human carcinogens

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Procarbazine and procarbazine hydrochloride are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals. The names "procarbazine" and "procarbazine hydrochloride" are used interchangeably in published studies; because only procarbazine hydrochloride is produced, it has been assumed that procarbazine hydrochloride was the substance under study.

Cancer Studies in Experimental Animals

Exposure to procarbazine hydrochloride by intraperitoneal injection caused tumors in rats and mice at several different tissue sites. In both rats and mice, it caused cancer of the brain (olfactory neuroblastoma) and hematopoietic system (lymphoma in rats and lymphoma or leukemia in mice). In rats, it also caused mammary-gland cancer (adenocarcinoma) in both sexes. In mice, it also caused benign lung tumors (adenoma) in both sexes and uterine cancer (adenocarcinoma) in females (NCI 1979).

Since procarbazine hydrochloride was listed in the *Second Annual Report on Carcinogens,* it has been reviewed several times by the International Agency for Research on Cancer, which identified additional studies in experimental animals. Administration of procarbazine hydrochloride by stomach tube caused tumors at some of the same tissue sites observed for intraperitoneal injection: leukemia and benign lung tumors (adenoma) in mice of both sexes and mammary-gland cancer (carcinoma or adenocarcinoma) in female rats. In other studies in rats, transplacental exposure caused cancer of neural tissue (neurinoma), and administration by intravenous injection caused tumors in various organs (mainly kidney tumors and intra-abdominal spindle-cell sarcoma). In rhesus and cynomolgus monkeys, exposure to procarbazine hydrochloride by several routes (orally or by intraperitoneal, subcutaneous, or intravenous injection) resulted in the development of acute myelogenous leukemia or lymphoma, blood-vessel cancer (hemangiosarcoma in the kidney), and bone cancer (osteosarcoma) in both sexes of both species (IARC 1981, 1982, 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to procarbazine hydrochloride. Procarbazine is used mainly in combination with other chemotherapeutic agents for the treatment of Hodgkin's lymphoma; it has been used historically in combination chemotherapy with mechlorethamine (nitrogen mustard), Oncovin (vincristine), and prednisone (MOPP) and more recently with other chemotherapeutic agents. MOPP was associated with acute non-lymphocytic leukemia in a number of studies (IARC 1981); however, these studies did not permit conclusions to be drawn about the independent effects of procarbazine and nitrogen mustard.

Since procarbazine hydrochloride was listed in the *Second Annual Report on Carcinogens,* additional studies in humans have been identified. In most cases, nitrogen mustard (nitrogen mustard hydrochloride), which is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen,* or its derivative melphalan, which is listed as *known to be a human carcinogen*, also was administered (IARC 1987). Some studies reported increased risks of secondary hematologic cancer after treatment with various procarbazine-containing regimens that did not include nitrogen mustard or melphalan (Tucker *et al.* 1988, Kaldor *et al.* 1990, Hoppe 1992, Schellong *et al.* 1997, Brusamolino *et al.* 1998), but the independent effect of procarbazine could not be evaluated. However, in a large case-control study, procarbazine (but not nitrogen mustard) was associated with significantly increased risks of leukemia and cancer of the bones, joints, cartilage, and soft tissues in models adjusting for exposure to other drugs (Boice *et al.* 1995). No association between procarbazine treatment and breast-cancer risk was observed among women with secondary breast cancer following treatment for Hodgkin's lymphoma (Travis *et al.* 2003, 2005).

Properties

Procarbazine hydrochloride is a methylhydrazine derivative (NCI 1979) that exists at room temperature as a white to pale-yellow crystalline powder with a slight odor. It is soluble in water, methanol, chloroform, and diethyl ether and is sensitive to oxidation (IARC 1981). Physical and chemical properties of procarbazine hydrochloride are listed in the following table.

Property	Information
Molecular weight	257.8[a]
Melting point	223°C[b]
Log K_{ow}	–1.69[a]
Water solubility	29.4 g/L at 25°C[a]
Vapor pressure	1.01×10^{-11} mm Hg at 25°C[a]

Sources: [a]ChemIDplus 2009, [b]Akron 2009.

Use

Procarbazine hydrochloride is used in human medicine as an antineoplastic and chemotherapeutic agent. It is used in combination with other antineoplastic agents such as nitrogen mustard, vincristine, and prednisone to treat Hodgkin's disease. In the MOPP regimens, the recommended dose for adults is 100 mg/m^2 for 10 to 14 days (IARC 1981).

Production

In 2009, procarbazine hydrochloride was produced by two U.S. manufacturers (HSDB 2009). Three U.S. suppliers were identified for procarbazine hydrochloride and one U.S. supplier for procarbazine (ChemSources 2009). No other data on U.S. production, imports, or exports of procarbazine hydrochloride were found. Procarbazine hydrochloride is the active ingredient in one pharmaceutical product approved by the U.S. Food and Drug Administration (FDA 2009).

Exposure

The routes of potential human exposure to procarbazine hydrochloride are ingestion, inhalation, and dermal contact (HSDB 2009). For patients receiving procarbazine hydrochloride as a chemotherapeutic agent, the typical initial dose of is 2 to 4 mg/kg of body weight daily, given orally in divided doses for 1 week, then 4 to 6 mg/kg daily until signs of bone-marrow depression occur. After bone-marrow recovery, treatment is resumed at a daily dose of 1 to 2 mg/kg (IARC 1981).

Occupational exposure to procarbazine hydrochloride could occur during manufacture, formulation, or packaging of the drug product. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,328 workers, including 289 women,

potentially were exposed to procarbazine hydrochloride (NIOSH 1990). Health professionals, such as physicians, nurses, and pharmacists, and service workers, such as housekeepers, potentially are exposed to procarbazine hydrochloride during drug preparation, administration, and cleanup.

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Procarbazine hydrochloride is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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